Micromanaging the Classification of Colon Cancer: The Role of the microRNAome

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Recent advances in our understanding of the microRNAome (miRNAome) have provided further insights into the molecular pathogenesis of colorectal cancer and shown a potential role for miRNAs in distinguishing molecular subtypes. The mucosa-adenoma-carcinoma model can now integrate miRNAs into the known genetic alterations that drive the progression of colorectal neoplasia. Clin Cancer Res; 17(23); 7207–9. ©2011 AACR.

In a recently published issue of Clinical Cancer Research, Balaguer and colleagues (1) showed that hereditary cases of colorectal cancer (CRC) due to Lynch syndrome can be distinguished from sporadic tumors displaying microsatellite instability (MSI) on the basis of microRNA (miRNA) profiles. In this issue, Bartley and colleagues (2) used a similar high-throughput platform to examine miRNA expression patterns across matched samples of normal mucosa, adenomas with low- and high-grade dysplasia, and microsatellite stable (MSS) adenocarcinomas. Both works represent a step forward in the integration of miRNA biology into the molecular subclassification of CRC and the multistep genetic model of colorectal tumorigenesis (1, 2).

More than 2 decades ago, Fearon and Vogelstein (3) proposed a model of colorectal carcinogenesis that highlights the sequential somatic acquisition of genetic alterations that characterize the transitions from normal mucosa to an adenomatous colonic lesion and, finally, to carcinoma. This seminal description has served as the framework for establishing the molecular classification of CRC.

CRCs can be classified into 2 groups based on the source of genetic instability. Approximately 15% of colorectal tumors present with MSI, arising from either a germline mutation in one of the mismatch repair (MMR) genes (Lynch syndrome) or epigenetic inactivation of MLH1 (sporadic MSI). MMR deficiency reduces the ability of tumor cells to repair specific DNA errors that tend to occur more frequently within microsatellite tracts. The accumulation of secondary mutations in coding microsatellite sequences will generate further genetic instability, thus promoting rapid cell growth, activation of transcription factors, deficiency of other DNA repair mechanisms, and inhibition of apoptosis (4). Therefore, this pathway of tumor development is called the mutator phenotype (4). In contrast, ~85% of CRCs are characterized by larger structural abnormalities in the genome, such as somatically acquired gains and losses (i.e., the chromosomal instability pathway). These tumors are almost always MSS and conform to the classic adenoma-to-carcinoma progression model (4). These cancers arise from an adenomatous lesion that early in its natural history acquired a somatic mutation in the APC gene or another component of the canonical Wnt pathway, such as CTNNB1, AXIN1, AXIN2, or TCF4 (5).

Genetic alterations classically described in CRCs, such as KRAS and PIK3CA mutations and loss of 18q and 17p, are frequently observed in later stages of tumor development in the chromosomal instability pathway (Fig. 1). This molecular classification has largely driven basic and clinical research in CRC during the last 20 years. For example, multiple studies characterizing the mutational profile of these tumor groups have shown that KRAS alterations are more frequently observed among MSS tumors, whereas BRAF and PIK3CA are present in MSI CRCs. Moreover, investigators have identified expression profiles for both tumor subtypes using high-throughput techniques (4).

Finally, several research groups recently uncovered the role of miRNAs in the biology of CRCs (6).

miRNAs are important posttranscriptional regulators that are ~18 to 24 nucleotides long. These short, noncoding RNAs bind to the 3’ untranslated regions of their target messenger RNAs (mRNA) and repress their expression. On the basis of bioinformatics and cloning studies, researchers have estimated that miRNAs may regulate 30% of all human genes. Furthermore, one miRNA may target hundreds to thousands mRNAs (5). Dysregulation of miRNAs has been detected in CRCs (7) and premalignant colonic lesions with the use of high-throughput platforms (8). In addition, investigators have identified different patterns of serum
miRNAs in patients with CRCs compared with healthy controls, thus suggesting their potential role not only in the prognostic setting but also in diagnostic and screening contexts (8). Differences in miRNA abundance observed in CRCs may be attributable directly to differential expression of the primary transcripts; however, other factors may play a role in these profiles (5). First, altered miRNA expression may be a consequence of tumor development that reflects the altered growth and differentiation properties of cancer cells compared with normal cells. Second, somatic mutations in oncogenes and tumor suppressor genes present in CRCs may influence patterns of miRNA expression by dysregulating their processing and cell dynamics. Although the impact of these alterations remains to be defined, it is known that TP53 mutations may exert specific effects on processing miRNAs. Finally, the impact of recurrent chromosomal lesions on miRNA dysregulation is a subject of ongoing research in the field (5).

Balaguer and colleagues (1) identified an miRNA profile that can differentiate tumors diagnosed in Lynch syndrome from sporadic MSI CRCs. Until recently, CRCs with MSI were considered clinically equivalent regardless of whether they arose sporadically or within Lynch syndrome. However, the clinical and therapeutic differences between these 2 MSI subgroups are becoming much clearer. As an example, MSI tumors more frequently harbor BRAF mutations, which have been associated with worse survival outcomes and lack of benefit from antiepidermal growth factor receptor therapies (9). Furthermore, it was recently observed that MSI tumors arising in patients diagnosed with Lynch syndrome may have a different sensitivity to 5-fluorouracil (10). Therefore, the data presented in the study by Balaguer and colleagues (1) identified an miRNA profile that can differentiate tumors diagnosed in Lynch syndrome from sporadic MSI CRCs.

Figure 1. Genetic model of CRC. Classical adenoma-to-carcinoma sequence and the 2 main genetic instability pathways for colorectal tumorigenesis. Genetic alterations along with the contribution of the miRNAome to the model are displayed. Modified from Vilar and Gruber (4), Fearon (5), and Slaby et al. (13). CIMP, CpG island methylator phenotype.
colleagues may guide further studies of the molecular mechanisms that account for these differences.

Another interesting observation from the work of Balaguer and colleagues is that patients with a clinical suspicion of Lynch syndrome but no identifiable mutation showed patterns of miRNA expression similar to those observed in patients with known germline mutations. It is well known that a significant proportion of patients who fulfill the clinical Amsterdam criteria for Lynch syndrome do not exhibit identifiable mutations in MMR genes. Several groups recently described additional molecular alterations that lead to MMR deficiency through complex genetic mechanisms. Such mechanisms include the inheritance of MLH1 germline epimutations (11) or deletion of the gene TACSTD1, upstream of MSH2, in combination with methylation of the MSH2 promoter in EpCAM-positive cells (12). In silico analysis of the miRNAs that are dysregulated in both subgroups of hereditary CRCs but are differentially expressed in sporadic MSI tumors may identify gene targets to explore as possible molecular mechanisms responsible for Lynch syndrome.

In another important study, Bartley and colleagues focused on MSS CRCs (2). Tumors that display chromosomal instability are an ideal setting in which to study the regulatory contribution of miRNAs to the mucosa-adenoma-carcinoma sequence. Bartley and colleagues established the dynamics of miRNA expression using matched samples from 20 MSS tumors, their corresponding normal mucosa, and adenomas showing different grades of dysplasia. The authors also classified miRNAs into 5 groups depending on the evolution of their expression across lesions (early versus late, and continuous versus intermittent patterns). The identification of miRNAs acting on the Wnt and ERK pathways confirms the role of miRNAs in the regulation of these 2 major pathways of colorectal tumorigenesis (13). These findings may be applicable to prognostic assessments for identification of lesions that harbor greater malignant potential. In fact, clinical application of this technology is feasible because miRNAs are more stable and less degraded in formalin-fixed, paraffin-embedded samples compared with DNA or RNA. Furthermore, these findings reinforce the promising future of targeting the Wnt pathway in CRC for therapy and chemoprevention (14). Therefore, the ability to micromanage miRNAs in CRC may open new avenues for translational research in the fields of diagnosis, prognosis, and therapeutic and chemopreventive interventions, and it highlights the general principle that a fuller understanding of molecular pathogenesis will open new horizons for cancer care.

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